

METRAZOL ACTIVATION OF THE ELECTROENCEPHALOGRAM IN PSYCHIATRIC PATIENTS*

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FOR many years diverse methods have been used to verify the diagnosis of epilepsy. Prior to the development of the electroencephalogram such methods as hydration-pitressin and hyperventilation were favored. Since the inception of the electroencephalogram, other methods of stress have been tried but most recently techniques involving the use of metrazol have found favor. Such variations include intramuscular or intravenous administration given slowly or rapidly with a considerable range of dosage. Among investigators who have had a wide experience with metrazol, Cure, Rasmussen and Jasper,¹ and Merlis, Henriksen and Grossman² favor slow intravenous injection whereas Cohn³ and A. E. Walker⁴ administer the drug rapidly. Many find metrazol particularly efficacious in localizing epileptogenic foci. Other aspects of metrazol investigation have prompted interest. Ziskind and Bercel⁵ for example have attempted to find a convulsive threshold. They have used metrazol to elicit what they call a minimal electroencephalographic response and found that these changes can be produced with smaller dosages in the epileptic than in the non-epileptic population. Other more complicated studies have been done, particularly those employing photic stimulation in conjunction with metrazol administration. This method has been especially recommended by Gastaut.⁶

A considerable body of knowledge has accumulated from the data. While Janz,⁷ Duensing⁸ and others feel that metrazol stimulation affords no value as a diagnostic tool in suspected epilepsy, in the hands of most investigators it would appear that individuals with epilepsy are more sensitive to this medication, showing epileptic wave patterns with much smaller dosages than are necessary in non-epileptic individuals.

Our interest in metrazol activation, however, was not aroused by

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experience with epileptic patients, but rather by two other observations. In the Payne Whitney Psychiatric Clinic electroencephalographic tracings are done routinely on each admission within forty-eight hours. The results of these tests show that for example approximately 15 per cent of all admissions in 1951 manifested mildly to moderately abnormal brain wave changes in the absence of neurological disease, previous electric shock or insulin therapy or in the presence of heavy sedation. First of all, we were interested in studying such patients with metrazol and comparing them with a control group who had shown no such abnormalities. The second group tested were patients who fitted into the "epileptoid" type of psychopathological reactions previously reported by Rockwell, Sherfey and Diethelm.⁹ These were individuals, who in the development of their psychiatric illnesses, complained that in the presence of anxiety they experienced recurrent episodic attacks of unreality feelings and depersonalization. These were characterized by disturbances in the perception of either a) the environment or b) themselves. Such complaints were verbalized as follows: That various parts of the body seemed larger or smaller, that their voices sounded unusually loud, hollow or far away. Others complained that objects at these times appeared strange, distorted, smaller or larger, out of focus or two dimensional, or that colors were particularly vivid. Associated with these complaints was a very marked thinking difficulty. Some gave a history of attacks of rage and even destructiveness following minor provocation. These symptoms were present throughout their lives but to a much lesser degree and it was not until the development of the present illness that they became greatly troubled by them. We determined to investigate this problem because these attacks resembled in many ways the disturbances frequently observed in epileptic patients and called these "epileptoid" because of the episodic nature and resemblance to complaints in epileptic individuals. Although the term "epileptoid" has been variously applied in the past, in this presentation, it is limited solely to those individuals who demonstrated the psychopathological manifestations described above.

PROCEDURE

Fifty-one patients used in this study were selected largely from the in-patient service, but also from the out-patient department of the Payne Whitney Psychiatric Clinic. Each patient had on a prior occasion re-

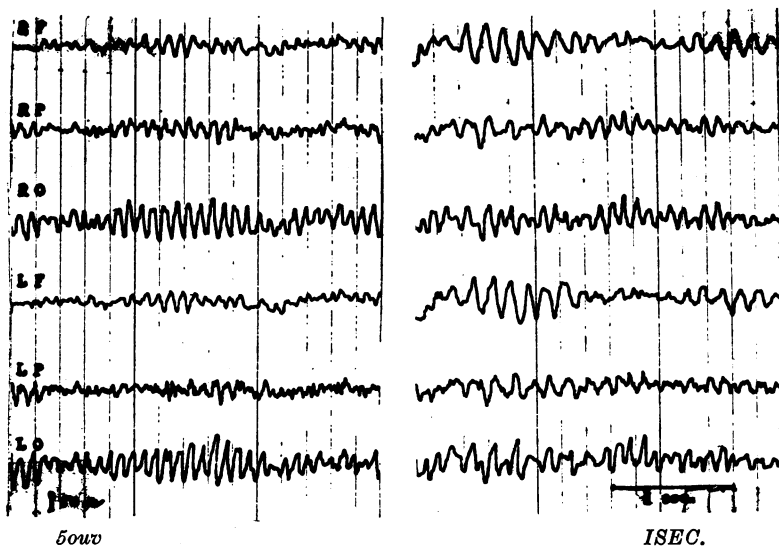


Figure 1. Normal tracing on left compared with moderately abnormal response on right.

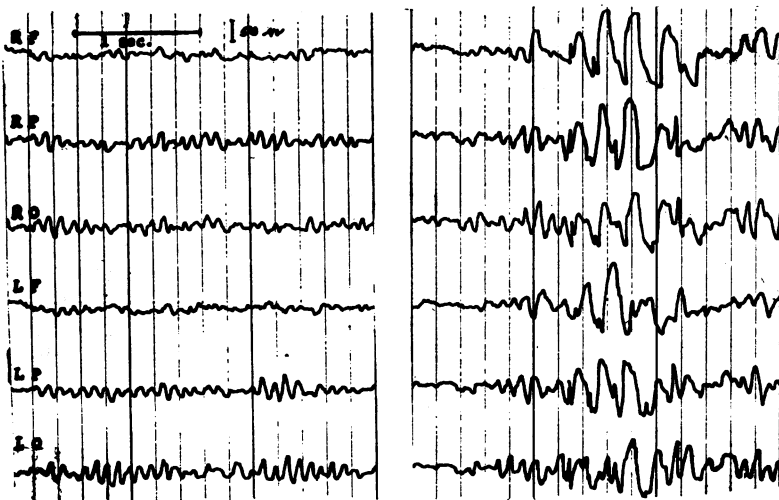


Figure 2. Normal tracing on left compared with markedly abnormal response on right.

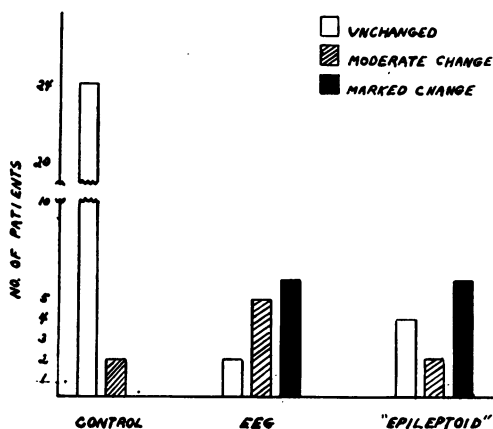


Figure 3. Results of metrazol activation showing the number of patients and type of response in each category.

ceived an electroencephalogram using 12 monopolar and bipolar leads, and had been subjected to 5 minutes of hyperventilation. For the metrazol examination a standard six channel Grass electroencephalogram was used and monopolar leads were placed in the frontal, parietal, and occipital area with yoked ear electrodes. Patients were given a standard meal prior to the test and a baseline tracing was obtained. An intravenous injection was instituted, consisting of 400 mg. of metrazol, diluted to 20 cc., so that each cc. contained 20 mg. of the drug. The metrazol was administered at a rate of 1 cc. or 20 mg. every 30 seconds until a total of 400 mg. had been given. In those instances where less than 400 mg. were given, the injection was stopped because of the appearance of epileptiform wave patterns or grand mal seizures. At the termination of the injection, patients were asked to hyperventilate for two minutes. After this, the recording was continued until the baseline pattern was obtained.

RESULTS

The various figures presented illustrate the changes which we consider abnormal as well as the changes which occur under the influence of metrazol.

The first two figures represent samples of electroencephalographic tracings in accordance with which our criteria for normal, moderately abnormal and severely abnormal were classified.

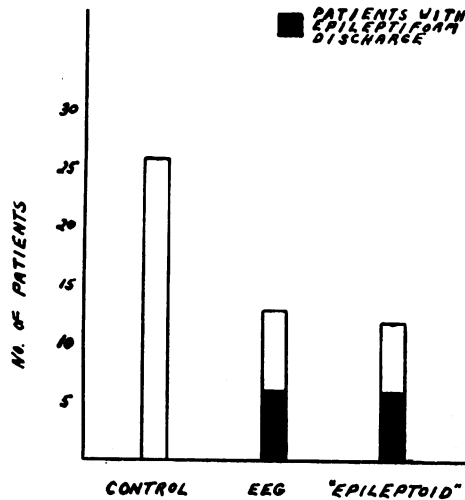


Figure 4. Number of patients with epileptiform discharge in each category.

In the third figure the clear bars represent the number of patients whose electroencephalograms were not influenced by metrazol. The obliquely shaded bars represent those patients who had a moderately abnormal response to the injection. The black bars represent the number of patients who had grossly abnormal responses.

Of the twenty-six in the control group, namely those patients whose baseline tracing showed no electroencephalographic disturbance, and who demonstrated no "epileptoid" features, twenty-four showed no further electroencephalographic changes while two showed moderately abnormal responses to metrazol. Of the thirteen patients tested because of moderate electroencephalographic abnormalities (indicated in Fig. 3 as EEG), and whose clinical history did not reveal "epileptoid" features, two showed no further changes with metrazol, five showed moderately increased abnormal responses, and six showed epileptiform wave patterns. Twelve patients were tested because of "epileptoid" psychopathological features and four of these showed no further change with metrazol while two showed moderately abnormal response, and six showed epileptiform discharge.

The fourth figure represents the numbers of patients whose abnormal responses consisted of 1) grand mal convulsions or 2) epileptiform discharge of atypical spike and wave variety in the electroencephalogram

TABLE I.—DIAGNOSTIC GROUPINGS.

	<i>Control</i>	<i>EEG</i>	<i>"Epileptoid"</i>
Manic-Depressive	1	—	—
Schizophrenia	3	4	6
Psychoneurosis	15	7	4
Psychopathic Personality	4	1	2
Paranoid Illness	1	—	—
Depression in Aging Period	2	1	—
Total	26	13	12

without a convulsion. The black shaded area of the bar shows the number of patients in each group who manifested such reactions. In the control group of twenty-six patients there were no convulsions or spike and wave phenomena. Of the patients tested with metrazol because of electroencephalographic abnormalities, six out of thirteen had abnormal brain wave changes of epileptiform character, two having an actual grand mal seizure. Of the twelve patients in the "epileptoid" group, six had epileptiform discharge with metrazol, one of whom had a seizure.

Of these three patients who developed grand mal seizures with metrazol, each showed some electroencephalographic abnormality on routine testing which was not diagnostic of an epileptic disorder. In one case metrazol helped to establish the diagnosis of epilepsy. In the second instance some believed the patient was epileptic because of the response to metrazol and the history of a single convulsion at 6 years of age. In the third case the reason for the convulsion was unclear.

Table I shows the breakdown of diagnoses and the number of patients in each category according to diagnosis.

DISCUSSION

The results of these studies show that there are very definite and marked differences in the way in which a control group of psychiatric patients respond to the slow intravenous injection of metrazol, when compared to patients who either a) show psychopathological manifestations described above as "epileptoid," or b) have minor electroencephalographic disturbances not otherwise explained by neurological or clinical psychopathological symptoms.

A few historical facts about the electroencephalogram in psychiatric disorders warrant mention. In general, there has been considerable work by a number of investigators regarding the presence of electroencephalographic abnormalities in various psychiatric disorders. First, in regard to schizophrenic patients, Davis and Davis,¹⁰ MacMahon and Walter¹¹ and Gibbs, Gibbs and Lennox¹² noted a high percentage of abnormalities. Next in the diagnostic category, psychopathic personality, Hill and Watterson,¹³ Knott and Gottlieb¹⁴ and Silverman,¹⁵ for example, have reported percentages variously ranging from 48 to 75 of abnormal electroencephalograms. The type of abnormality generally found was an excess of slow waves. Finally, in psychoneurotic individuals of the obsessive-compulsive variety, as investigated by Rockwell and Simons,¹⁶ electroencephalographic abnormalities were found in thirteen out of twenty-four patients.

It would appear then that these investigations have led to no consistent conclusions, since a common denominator has not been found to explain these observations. We know only that psychiatric patients regardless of diagnosis can show abnormal brain waves more frequently than the so-called normal population. Historically and with particular pertinence to this study one other report bears mention. In 1941 Diethelm and Simons,¹⁷ in a study of five psychiatric cases, found electroencephalographic disturbances and psychopathological symptoms which were later labelled by Rockwell, Sherfey, and Diethelm as "epileptoid."

In this study the results of metrazol activation, in addition to substantiating the observation of others that abnormal brain wave changes can be observed in certain psychiatric disorders, further demonstrate some specificity. In the "epileptoid" group, where episodic complaints similar to those seen in epileptics are prominent, a high percentage of sensitivity to metrazol was apparent. In the second group of subjects, tested because of electroencephalographic abnormalities, metrazol helped to clarify the diagnosis of epilepsy where the disorder was suspected but uncertain. Yet in the remainder of these patients, even though the diagnosis of epilepsy could not be contemplated, there was a greater sensitivity to metrazol than in a control group. This still leaves us with a number of individuals who do not fall into any particular diagnostic or clinical category. There may be many other factors to explain these observations. Ostow and Ostow¹⁸ in their work, mention possible con-

genital and familial factors. Others, such as Cohn and Nardini,³ have emphasized the aggressive personality features of patients unusually sensitive to metrazol. Frustrated aggressive impulses have also been postulated to explain grand mal seizures. On the other hand, Ferenczi¹⁹ suggests that the epileptic attack might be considered as regression to the infantile period of wish fulfillment by means of uncoordinated movements. However, the relationship between pathophysiological changes and psychodynamics is difficult to evaluate and remains a provocative question.

If the electroencephalogram is to be considered as a valid tool for investigation, or for making observations about human cortical physiology in psychiatric disorders, a new approach for such investigative work must be found. Metrazol as an investigative tool may give us some insight into the problem but there is need for more detailed clinical and laboratory study.

SUMMARY

1. Slow intravenous injection of metrazol in fifty-one psychiatric patients showed only a mild amount of change in two out of twenty-six control patients. In the "epileptoid" group four showed no changes, two showed mild changes, five showed spike and wave response and one had a convulsion. In those patients who had mild changes in their electroencephalograms prior to metrazol, two showed no response, five showed mild response and six showed spike and wave formation of whom two had convulsions.

2. Metrazol activation of the electroencephalogram elucidated a little more clearly the significance of the electroencephalographic findings in certain psychiatric patients. The significance has been discussed and further intensive study of both the psychopathology and pathophysiology in additional psychiatric subjects is indicated.

REFERENCES

1. Cure, C., Rasmussen, T. and Jasper, H. Activation of seizures and electroencephalographic disturbances in epileptic and in control subjects with "metrazol," *Arch. Neurol. Psychiat.* 59:691-717, 1948.
2. Merlis, J. K., Henriksen, G. F. and Grossman, C. Metrazol activation of seizure discharges in epileptics with normal routine electroencephalograms, *Electroencephalog. clin. Neurophysiol.* 2: 17-22, 1950.
3. Cohn, R. and Nardini, J. E. Spike-dome discharges in selected psychiatric patients activated by intravenous metrazol (abstract), *Proc. Amer. EEG Soc.*

- Electroencephalog. clin. Neurophysiol.* 3: 383, 1951.
4. Walker, A. E. *Posttraumatic epilepsy*. Springfield, Ill., C. C. Thomas, 1949.
 5. Ziskind, E. and Bercel, N. A. Preconvulsive paroxysmal electroencephalographic changes after metrazol injection, in *Epilepsy*, Association for Research in Nervous and Mental Diseases, Research publications, v. 26, 1947, pp. 487-501.
 6. Gastaut, H. Combined photic and metrazol activation of brain, *Encephalog. clin. Neurophysiol.* 2:249-61, 1950.
 7. Janz, H. W. Zur diagnostischen Verwertbarkeit der Cardiazolkrämpfe, *Münch. med. Wschr.* 84:471, 1937.
 8. Duensing, F. Darf der Cardiazol-Krampfanfall diagnostisch verwertet werden? *Münch. med. Wschr.* 84:1011-15, 1937.
 9. Rockwell, F. V., Sherfey, M. J. and Diethelm, O. Epileptoid psychopathologic reactions, in *Epilepsy*, Association for Research in Nervous and Mental Diseases, Research publications, v. 26, 1947, pp. 573-85.
 10. Davis, P. A. and Davis, H. Electroencephalograms of psychotic patients, *Amer. J. Psychiat.* 95:1007-25, 1938-1939.
 11. MacMahon, J. F. and Walter, W. G. Electro-encephalogram in schizophrenia, *J. ment. Sci.* 84:781-87, 1938.
 12. Gibbs, F. A., Gibbs, E. L. and Lennox, W. G. Likeness of cortical dysrhythmias of schizophrenia and psychomotor epilepsy, *Amer. J. Psychiat.* 95:255-69, 1938-1939.
 13. Hill, D. and Watterson, D. Electroencephalographic studies of psychopathic personalities, *J. Neurol. Psychiat.* 5:47-65, 1942.
 14. Knott, J. R. and Gottlieb, J. S. Electroencephalogram in psychopathic personality, *Psychosom. Med.* 5:139-42, 1943.
 15. Silverman, D. Clinical and electroencephalographic studies on criminal psychopaths, *Arch. Neurol. Psychiat.* 50:18-33, 1943.
 16. Rockwell, F. V. and Simons, O. J. Electroencephalogram and personality organization in obsessive-compulsive reactions, *Arch. Neurol. Psychiat.* 57:71-77, 1947.
 17. Diethelm, O. and Simons, D. J. Psychopathologic symptom group with pathologic electroencephalograms, *Trans. Amer. neurol. Assoc.* 67:224-25, 1941.
 18. Ostow, M. and Ostow, M. Bilaterally synchronous paroxysmal slow activity in electroencephalograms of non-epileptics, *J. Nerv. ment. Dis.* 103:346-58, 1946.
 19. Ferenczi, S. *Sex in psychoanalysis*. Boston, Gorham Press, 1916, p. 224.

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